Atty. Dkt. No. 029318-0615

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Bosch et al.

Title: LIQUID DROPLET AEROSOLS OF NANOPARTICULATE DRUGS

Appl. No.: 09/597,738

Filing Date: 06/19/2000

Examiner: M. Haghighatian

Art Unit: 1616

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AMENDMENT UNDER 37 C.F.R. § 1.111

Commissioner for Patents
Washington, D.C. 20231

Sir:

This communication is responsive to the Office Action dated October 2, 2002. While a shortened statutory period for response has expired, filed herewith is a Petition for a two month extension of time to extend the period for response to **March 2, 2003**. Accordingly, this response is timely filed.

REMARKS

Applicants respectfully request reconsideration of the present application in view of the reasons that follow.

I. Status of the Claims

Claims 51 – 119 are pending. Claims 51 – 64, 79 – 81, 84 – 101, 118, and 119 are under examination and claims 65 – 78, 82, 83, and 102- 117 are withdrawn from consideration.

II. Summary of the Claimed Invention

The claimed invention is directed to aerosols of liquid dispersions of nanoparticulate active agents (claims 51-64, 80, 81, and 118), methods of administering such aerosols to patients (claim 79), aerosols useful in a propellant-based pMDI (claims 84-100 and 19), and methods of administering

such propellant-based pMDI aerosols to patients (claim 101). The aerosols are useful for nasal delivery as well as lung delivery

The claimed aerosols comprise droplets of an aqueous dispersion of nanoparticulate active agent particles in which: (1) essentially each droplet of the aerosol comprises at least one nanoparticulate active agent particle; (2) each droplet has a diameter less than or equal to 100 microns; and (3) the nanoparticulate active agent particles have a size of less than about 1000 nm. This is not shown or suggested in the cited prior art.

The claimed invention is an improvement over the prior art, as prior to the present invention it was not know if liquid aerosols of nanoparticulate active agents could be designed in which *each aerosol droplet contains at least one nanoparticulate active agent particle.* This is significant, as droplets lacking active agent *significantly* decrease the effectiveness of the therapeutic composition. This is because if droplets of an aerosol do not contain active agent, such droplets essentially define part of the volume of the dosage to be given but lack any therapeutic effect.

III. Rejection of the Claims Under § 103(a)

Claims 51-64, 79-81, and 118 were rejected under 35 U.S.C. § 103(a) as being allegedly unpatentable over Wood et al., U.S. Patent No. 6,264,922 B1. Office Action at page 3. Applicants respectfully traverse this ground for rejection.

In addition, claims 51-64, 79-81, and 118 were rejected under 35 U.S.C. § 103(a) as being allegedly unpatentable over Wiedmann et al., U.S. Patent No. 5,747,001. Office Action at page 4. Applicants respectfully traverse this ground for rejection.

A. Summary of the Cited References

Wood et al. is directed to nebulized aerosols comprising droplets of an aqueous dispersion of nanoparticulate therapeutic or diagnostic agent particles. The droplets have a particle size of less than about 50 microns in diameter.

Wiedmann et al. describes aerosols comprising droplets of an aqueous dispersion of nanoparticulate beclomethazone particles.

B. The Cited References Do Not Teach or Suggest Applicants' Claims Directed to Aerosols of Liquid Dispersions in Which Each Droplet Contains at Least One Drug Nanoparticle

Applicants' claims directed to aerosols of liquid dispersions of nanoparticulate active agents are an improvement over prior art aerosols of liquid dispersions, such as those of Wiedmann et al. and Wood et al. This is because the prior art references fail to teach or suggest an aerosol in which essentially every droplet in contains at least one active agent nanoparticle.

This is significant, as aerosol droplets lacking active agent nanoparticles can create inconsistent active agent dosages. It is important that each dose of an aerosol contain approximately the same quantity of active agent. If this is not the case, the intended recipient can receive either too much or too little of the active agent. This particularly problematic for drugs which are frequently administered in aerosol dosage forms, such as asthma drugs, cystic fibrosis medications, seasonal or perennial rhinitis medications, vaccines, antiviral agents, and potentially insulin for diabetics.

1. Aerosol Asthma Medications

Asthma medications delivered via an aerosol include bronchodilators, anti-inflammatories, such as corticosteroids (*e.g.,* beclomethasone), and mast cell stabilizers. *See* "Asthma Medications," WebMD, http://my.webmd.com/content/article/10/1660_51069.htm?lastselectedguid={5FE84E90-BC77-4056-A91C-9531713CA348}. It is critical that dosage forms of such drugs have dose uniformity to ensure that subjects receive sufficient medication to alleviate the asthma symptoms without providing an excess amount of drug which can result in undesirable side effects. Such a need is met by Applicants' claimed invention, but not by the cited prior art references.

There are two main types of bronchodilator medications: Beta2-agonists (short- and long-acting forms) and anticholinergics. Beta2-agonists provide either relief (short-acting forms) or control (long-acting forms) of asthma symptoms. Inhaled forms of short-acting Beta2-agonists are rescue medications that relieve asthma symptoms very quickly. The long-acting forms of beta2-agonists are used for better control -- not for relief -- of asthma. Serevent® (salmeterol) and Foradil® (formoterol) are the only inhaled, long-acting beta2-agonists. They are used twice a day to maintain open airways for long term-control, specifically in the evening. Side effects of beta2-agonists include nervous or shaky feelings, overexcitement or hyperactivity, increased heart rate, and, rarely, upset stomach or trouble sleeping. Such side effects are also associated with administration of an excess amount of drug.

Inhaled corticosteroids work the best to reduce airway inflammation and mucus, which leads to better asthma control, with fewer symptoms and flare-ups. Dosages vary, and they need to be taken daily. Side effects will depend on the dose. At higher doses, thrush (yeast infection in the mouth) and hoarseness may occur. Again, it is highly desirable that the aerosol dosage forms deliver the proper amount of drug to provide relief of the asthma symptoms without providing an excess of drug which can result in undesirable side effects. Such a need is met by Applicants' claimed invention, but not by the cited prior art references.

2. Cystic Fibrosis Therapies

Cystic fibrosis is a generalized hereditary disorder associated with widespread dysfunction of the exocrine glands, with accumulation of excessively thick and tenacious mucus and abnormal secretion of sweat and saliva.

Medication therapy for cystic fibrosis includes antibiotics which can be inhaled directly into the lower respiratory tract for treatment of infections. Inhaled antibiotics do not have all of the same side effects as other methods of delivery, in part because the doses can be smaller. However, some inhaled antibiotics can irritate the lungs and cause a coughing reflex. Side effects of antibiotics include nausea or vomiting; mild diarrhea; another infection, often due to another kind of organism; skin rashes, hives, or itching; or severe allergic reaction (rare). *See* "Cystic Fibrosis Therapies; An Overview," WebMD, http://my.webmd.com/content/healthwise/122/30425.htm?lastselectedguid={5FE84E90-BC77-4056-A91C-9531713CA348}. Dose uniformity of an aerosol antibiotic is important as if the administered dose lacks sufficient drug, the infection may be prolonged, which is unhealthy for the patient. However, an excess of drug is also undesirable because of the side effects associated with antibiotics. Such a need for dose uniformity is met by Applicants' claimed invention, but not by the cited prior art references.

3. Aerosol Vaccines

A measles vaccine spray, delivered as a booster, has been found to be effective in clinical studies. *See* "Response to different measles vaccine strains given by aerosol and subcutaneous routes to schoolchildren: A randomised trial," *Lancet*; *355*(9206):798-803 (March 4, 2000). This could be particularly beneficial to developing countries. Specifically, this article reports that the aerosol route of administration is particularly suited to mass immunization campaigns because of its

cost-effectiveness and lack of a risk of infection associated with needles. In addition, such a dosage form is quick and easy to administer by workers with limited medical training. However, a key element of such a vaccine would be a dosage form that consistently delivered accurate dosages to prevent inadequate immunization or side-effects from over-dosage. Such a need is met by Applicants' claimed invention, but not by the cited prior art references

4. Aerosol Biologics

There are several current commercial aerosol biological dosage forms, as well as others being investigated for future use. For example, ribavirin is a synthetic nucleoside used as a broad-spectrum antiviral in the treatment of severe viral pneumonia caused by respiratory syncytial virus (RSV), particularly in high-risk infants with underlying conditions such as cardiopulmonary disease; administered by aerosol. Ribavirin has been shown to decrease the spread of RSV infection. However, side effects associated with the aerosol dosage form include rash and reddened eyes (conjunctivitis) after getting the medication by mist. *See* "Antiviral medications for respiratory syncytial virus (RSV) infection," WebMD, http://my.webmd.com/content/healthwise/76/18955.htm?lastselectedguid={5FE84E90-BC77-4056-A91C-9531713CA348}. It is important that the proper amount of antiviral agent be delivered to the patient to ensure the desired therapeutic effect without triggering unwanted side effects. Such a need is met by Applicants' claimed invention, but not by the cited prior art references.

Another example of an aerosol biological is aerosol insulin. *See* Laird Harrison, "New Ways to Take Insulin; Experimental Devices May Do Away With Daily Shots," WebMD Medical News (June 18, 2002) http://my.webmd.com/content/article/48/39241.htm?lastselectedguid={5FE84E90-BC77-4056-A91C-9531713CA348}. The article reports that several companies are developing insulin inhalers similar to those used to treat asthma. Such a dosage form is highly desirable, both for increased patient compliance with the elimination of injectable insulin, as well as a potential decrease in administration of excess insulin, which can put patients at greater risk of side effects such as heart disease. However, it is critical that a useful aerosol insulin dosage form provide dose uniformity. Applicant's claimed invention would aid development of such a dosage form, whereas the cited prior art does not address this issue.

C. Applicants' Claimed Invention is not Taught by the Cited References

Applicants' claimed invention overcomes the problem of poor dose uniformity present in the prior art, as essentially each droplet of the claimed aerosols of liquid dispersions contains at least one nanoparticulate active agent.

Accordingly, Wiedmann et al. and Wood et al. fail to teach or suggest Applicants' claims directed to aerosols of liquid dispersions of nanoparticulate active agents. Withdrawal of this ground for rejection is respectfully requested.

III. Conclusion

Applicants respectfully request reconsideration of this application in view of the above amendments and remarks. This application is now in condition for allowance and early notice to that effect is respectfully solicited.

Should the Examiner have any questions or comments regarding the pending application or this Amendment, the Examiner is requested to call the undersigned at 202-672-5538.

If there are any fees due in connection with the filing of this Amendment, please charge the fees to our Deposit Account No. 19-0741. If a fee is required for an extension of time under 37 C.F.R. § 1.136 not accounted for above, such an extension is requested and the fee should also be charged to our Deposit Account.

Respectfully submitted,

Date March 3, 2003 By Michele M. Simkin

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